46. (Amended) A method for treating or preventing osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis, which comprises administering to a mammal in need of such treatment an effective amount of a pharmaceutical formulation according to any one of claims 1 to 34.

A3 cont

Add new claim 47 as follows.

47. The pharmaceutical formulation according to claim 1, wherein the additive is a phosphonate derivative selected from the group consisting of DL-a-glycerophosphate, 3-amino-1-hydroxypropylidene-1,1-diphosphonate, diethyl maleate and diethylethoxymethylene malonate.

A4

REMARKS

The claims have been amended to bring the application into conformance with standard U.S. patent practice. Improper multiple dependent claims 37 and 38 have been canceled. Improper use-type claims 43 and 44 have also been canceled. The multiple dependency of each of dependent claims 30, 36, 39, 42, 45 and 46 has been further limited so that no multiple dependent claim depends on another multiple dependent claim. The claims have also been amended to more clearly and particularly recite the invention in accordance with U.S. patent practice. New claim 47 has been added to claim subject matter deleted as a result of amending claim 1.

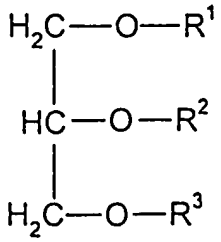
Please also note that in the following "Marked-Up Version Showing Revisions to the Claims", only the large, 16-point, bolded brackets indicate a deletion. The 12 point, "un-bolded" brackets appearing in claim 33 in the compound "1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene-1,1-bisphosphonic acid" are part of the chemical name of the compound and do not indicate a deletion.

No new matter has been added by any of the amendments to the claims.

MARKED-UP VERSION SHOWING REVISIONS TO THE CLAIMS

1. (Amended) A pharmaceutical formulation comprising at least one bisphosphonate and one or more of an additive agent, said additive agent being present in an amount sufficient to provide an enhanced absorption of the bisphosphonate, and said additive being [a substance] selected from the group consisting of

- a surfactant;
- an ampholytic surfactant;
- an anionic surfactant;
- a cationic surfactant;
- a bile salt;
- a soap and a fatty acid, and a salt thereof;
- a lipid with the exception of a medium chain glyceride or a mixture of medium chain glycerides having the formula



wherein R^1, R^2 and R^3 are the same or different and each represent a hydrogen atom or an alkanoyl chain having 6 to 18 carbon atoms, [preferably 6 to 12 carbon atoms, provided that] wherein at least one of [or] R^1, R^2 and R^3 is an alkanoyl group[.];

- an oil;
- an enamine;
- a chelating agent;
- a phenothiazine;
- a fatty acid derivative of carnitine or a peptide;
- a substance selected from the group consisting of azone, concanavalin A, a phosphate and a phosphonate derivative[, such as DL -a-glycerophosphate and 3-amino-1 hydroxypropylidene-1,1-diphosphonate, diethyl maleate and diethylethoxymethylene malonate];
- a product [from] of a Maillard reaction [reactions];
- a polymer[, such as a block copolymer and a biodegradable polymer];
- a chitosan and a chitosan derivative; and

– combinations thereof.

2. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a nonionic surfactant.

3. (Amended) The [A] pharmaceutical formulation according to claim 2, wherein the nonionic surfactant is a sugar glycoside or a sugar fatty acid ester.

4. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a lipid.

5. (Amended) The [A] pharmaceutical formulation according to claim 4, wherein the lipid is a phospholipid.

6. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is an oil.

7. (Amended) The [A] pharmaceutical formulation according to claim 6, wherein the oil is soy bean oil or sunflower oil.

8. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a chelating agent.

9. (Amended) The [A] pharmaceutical formulation according to claim 8, wherein the chelating agent is EDTA, EGTA or citric acid.

10. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a fatty acid derivative of carnitine or a peptide.

11. (Amended) The [A] pharmaceutical formulation according to claim 10, wherein the additive of the fatty acid derivative of carnitine or a peptide is palmitoyl-DL-carnitine.

12. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a polymer.

13. (Amended) The [A] pharmaceutical formulation according to claim 12, wherein the polymer is a polyacrylic acid.

14. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a block copolymer.

15. (Amended) The [A] pharmaceutical formulation according to claim 14, wherein the block copolymer is a poloxamer, a poloxamine or meroxapol.

16. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a saponin.

17. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a biodegradable polymer.

18. (Amended) The [A] pharmaceutical formulation according to claim 17, wherein the biodegradable polymer is polyactid acid or polyglycolic acid.

19. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid and a surfactant.

20. (Amended) The [A] pharmaceutical formulation according to claim 19, wherein the combination of the lipid and the surfactant is monoolein and sodium taurocholate, or monoolein and Tween 80.

21. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid of non-phospholipid character and a phospholipid.

22. (Amended) The [A] pharmaceutical formulation according to claim 21, wherein the combination of the lipid of non-phospholipid character and the phospholipid is a medium chain glyceride and a lecithin.

23. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a combination of a lipid and a block copolymer.

24. (Amended) The [A] pharmaceutical formulation according to claim 23, wherein the combination of the lipid and the block copolymer is monoolein and Pluronic F 127.

25. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a combination of a surfactant and an oil.

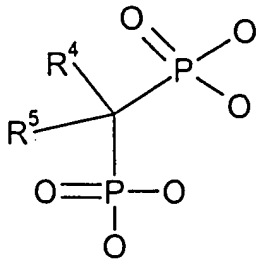
26. (Amended) The [A] pharmaceutical formulation according to claim 25, wherein the combination of the surfactant and the oil is a sucrose fatty acid ester and soy bean oil.

27. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein the additive is a combination of a polymer and a lipid.

28. (Amended) The [A] pharmaceutical formulation according to claim 27, wherein the combination of the polymer and the lipid is polycarbophil and monoolein.

29. (Amended) The [A] pharmaceutical formulation according to claim 1, wherein said additive is in the form of [the combination of additives is chosen to form] an emulsion or a microemulsion.

30. (Amended) The [A] pharmaceutical formulation according to claim 1, [any one of claims 1 to 29] wherein the [said] bisphosphonate has the formula II



II

wherein

R^4 is H, OH or Cl, and

R^5 is

(a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;

(b) halogen;

(c) arylthio or chlorosubstituted arylthio;

(d) cycloalkylamino with 5 to 7 carbons; or

(e) saturated five or six membered nitrogen containing, heterocyclyl with 1 or 2 heteroatoms.

31. (Amended) The [A] pharmaceutical formulation according to claim 30 wherein the bisphosphonate has the formula II

wherein

R^4 is H or OH and

R^5 is

(a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino, or heterocyclyl;

(d) cycloalkylamino with 5 to 7 carbons; or

(e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

32. (Amended) The [A] pharmaceutical formulation according to claim 30 wherein the bisphosphonate has

the formula II

wherein

R^4 is OH and

R^5 is

(a) alkyl with 1 to 6 carbon atoms, optionally substituted with amino, alkylamino, dialkylamino or heterocyclyl;

(d) cycloalkylamino with 5 to 7 carbons; or

(e) saturated five or six membered nitrogen containing heterocyclyl with 1 or 2 heteroatoms.

33. (Amended) The [A] pharmaceutical formulation according to claim 30 wherein the bisphosphonate is selected from the group consisting of:

4-amino-l-hydroxybutylidene-1,1-bisphosphonic acid (alendronate),

N,N-dimethyl-3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (mildronate, olpadronate),

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid (ibandronate),

1-hydroxy-2-(3-pyridyl)ethylidene-1,1-bisphosphonic acid (risedronate),

1--hydroxyethylidene-1,1-bisphosphonic acid (etidronate),

1-hydroxy-3-(1-pyrrolidinyl)propylidene-1,1-bisphosphonic acid,

1-hydroxy-2-(1-imidazolyl)etylidene-1,1-bisphosphonic acid (zoledronate),

1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethylidene-1,1-bisphosphonic acid (minodronate),

1-(4-chlorophenylthio)methylidene-1,1- bisphosphonic acid (tiludronate),

1-(cycloheptylamino)methylidene-1,1-bisphosphonic acid (cimadronate, incadronate),

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate) and pharmaceutically acceptable salts thereof.

34. (Amended) The [A] pharmaceutical formulation according to claim 33 wherein the bisphosphonate is alendronate (4-amino-1-hydroxybutylidene-1,1-biphosphonic acid) or a pharmaceutically acceptable salt [salts] thereof.

35. (Amended) The [A] pharmaceutical formulation according to any one of claims 1 to 34, wherein the formulation [which] is adapted for oral administration.

36. (Amended) The [A] pharmaceutical formulation according to any one of claims 1 to 34, wherein the formulation [1-35 which] is adapted for non colonic delivery.

39. (Amended) The [A] pharmaceutical formulation according to any one of claims 1 to 34, [of the preceding claims] wherein the formulation is in particulate form.

40. (Amended) The [A] pharmaceutical formulation according to claim 39 wherein the particulate form is solid or semisolid.

41. (Amended) The [A] pharmaceutical formulation according to claim 39 or 40, [any of claims 39 and 40] wherein the bisphosphonate [bisphosphone] is in the form of micronized powder.

42. (Amended) A process for the preparation of a pharmaceutical formulation according to any one of claims 1 to 34, [40,] comprising forming a mixture of (i) at least one bisphosphonate, (ii) an additive and (iii) a pharmaceutically acceptable carrier.

45. (Amended) A method for inhibiting [inhibition of] bone resorption which comprises administering to a mammal[, including man,] in need of such treatment an effective amount of a pharmaceutical formulation according to any one of claims 1 to 34 [41].

46. (Amended) A method for treating or preventing [the treatment and prevention of] osteoporosis and bone loss related to age, steroid therapy, rheumatism, Paget's disease, cancer, secondary osteoporosis except steroid induced osteoporosis, periodontitis or osteoarthritis, which comprises administering to a mammal[, including man,] in need of such treatment an effective amount of a pharmaceutical formulation according to any one of claims 1 to 34 [41].

CONCLUSION

Upon entry of this Preliminary Amendment, claims 1-36, 39-42, and 45-47 are pending and in condition for allowance, which action is earnestly solicited. No fee should be due in connection with filing this Preliminary Amendment. However, should any fee be deemed necessary, the Assistant Commissioner is hereby authorized to charge Deposit Account No. 23-1703.

Dated: October 5, 2001

Respectfully submitted,

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